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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,047	JESSBERGER ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,10-19,29-32,34-44,48,49,134,139 and 140* is/are pending in the application.

4a) Of the above claim(s) *139 and 140* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10-19,29-32,34-44,48,49 and 134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-6-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of claims 1-2, 10-19, 29-32, 34-44, 48-49, and 134 drawn to a method of inducing infertility in an animal comprising administering an antisense oligonucleotide in the reply filed on August 29, 2008 is acknowledged. The traversal is on the ground(s) that there is no serious burden to search all pending claims. This is not found persuasive because the alleged issue of search burden was neither addressed nor stated in the Office action dated February 29, 2008. Note that the restriction was required on the basis of a single general inventive concept and special technical features under PCT Rule 13.1 and PCT Rule 13.2

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Currently, claims 1-2, 10-19, 29-32, 34-44, 48-49, 134, and 139-140 are pending. Claims 139-140, small molecule, peptidomimetic, antibody are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Accordingly, claims 1-2, 10-19, 29-32, 34-44, 48-49, and 134 pertaining to an antisense oligonucleotide is under examination on the merits.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on November 6, 2006 is being considered by the examiner, except the information contained in C53-C64. Note that each of the NCBI Database GenBank accession numbers in C53-C64 must be accompanied by appropriate publication dates.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 134 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 134, the phrase "substantially as described and illustrated herein" renders the claim indefinite because it is unclear what is meant by "herein". Note that a claim is not a description or an illustration. Since it is vague and unclear what "herein" refers to in claim 134, one of ordinary skill in the art cannot ascertain the metes and bounds set forth in claim 134, thereby rendering the claim indefinite. For examination purpose, the claim will be interpreted to mean a method as claimed in claim 1 or claim 10.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 10-19, 29-32, 34-38, 40-44, 48-49, and 134 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods for inhibiting meiosis in germ cells by using an antisense SMC1β nucleic acid molecule, does not reasonably provide enablement for *in vivo* methods for inducing infertility in an animal or inhibiting meiosis in an animal by administering an antisense SMC1β nucleic acid molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Below are the factors analyzed to determine the enablement requirement.

(A) The breadth of the claims

Claims 1-2, 10-19, 29-32, 34, 40-42, and 134 are strictly drawn to *in vivo* methods for inducing infertility or inhibiting meiosis in an animal including human, comprising administering an antisense SMC1β nucleic acid molecule to said animal, wherein the antisense molecule functions as a contraceptive agent. Claims 35-38, 43-44, and 48-49 embrace *in vivo* methods of administering an antisense SMC1β nucleic acid molecule to an animal.

(B) The nature of the invention

The instantly claimed invention is characterized as antisense-mediated gene therapy.

(C) The state of the prior art

The earliest filing date sought in the instant application is August 29, 2003. The state of the prior art pertaining to gene therapy utilizing antisense molecules for inducing infertility by administering the molecules to a living animal was underdeveloped as evidenced by the lack of published references teaching that inhibiting SMC1β expression by antisense technology is effective in inducing infertility or inhibiting meiosis in the subject. Furthermore, although SMC1β was known to regulate meiosis or chromosome dynamics prior to the date of the invention was made (see for example applicant's citation No. C73), the direct link or nexus between the absence of SMC1β expression and infertility was not established in the art as of the earliest filing date sought in the instant case. In addition, there is no prior art of record that teaches appropriate guidelines to practice gene therapy for inducing infertility or inhibiting

meiosis in a human as claimed in the instant case. Therefore, the state of the prior art commensurate in scope with the instantly claimed invention was not well regarded at the time of the invention.

(D) The level of one of ordinary skill

Due to the lack of prior art teachings concerning either the use of antisense technology in an animal to induce infertility or the correlative relationship between SMC1β and fertility, one of ordinary skill in the art would not have known whether application of antisense agents targeted against SMC1β would indeed induce infertility by blocking spermatogenesis or oogenesis in the animal as claimed in the instant case. Further, since the gene therapeutic technology such as the claimed antisense technology for regulating meiosis in an animal by administering the antisense agents to the testis or ovary, wherein the antisense molecule is used as a contraceptive agent was considered nascent as detailed above, one of ordinary skill in the art would not have known how to practice the entire scope of the claimed gene therapeutic methods without having specific guidance from the inventor or performing undue experimentation.

(E) The level of predictability in the art

As of the earliest filing date sought in the instant application, inhibiting target gene expression via nucleic acid molecules with requisite therapeutic effects was considered highly unpredictable in an animal *in vivo*. See Opalinska et al. (*Nature Reviews,* 2002, 1:503-514). On page 511, Opalinska et al. teach the unpredictability of nucleic acid molecules to inhibit the expression of their intended targets *in vivo* as following: "Nucleic-acid-mediated gene silencing

has been used with great success in the laboratory, and this strategy has also generated some encouraging results in the clinic. Nevertheless, it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA....Accordingly, mRNA targeting is largely a random process, which accounts for the many experiments in which the addition of an antisense nucleic acid yields no effect on expression." (emphasis added).

The unpredictability of *in vivo* inhibitory activity of antisense molecules remained unresolved even after the earliest filing date sought in the instant case as evidenced by a post-dated reference (Patil et al., *American Association of Pharmaceutical Scientists Journal,* 2005, 7(1):E61-E77). Patil et al. warn against extremely low success of the introduction of DNA-based drugs for *in vivo* use. See page E62 for example, wherein Patil et al. teach the following: "Despite many favorable characteristics and signs of possible clinical victories (see Table 1), the introduction of DNA-based drugs for human use can be best described as limited, with rare successes. The inertia in the development of these drugs can be attributed, in part, to their poor cellular uptake profile *in vivo.* The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half-life result in unpredictable pharmacokinetics...The resulting random delivery profile of DNA-based drugs is further complicated by a lack of *in vivo/in vitro* correlation of their pharmacological outcomes."

As evidenced by the teachings of Opalinska et al. and Patil et al., delivering antisense oligonucleotides into an appropriate target cell or tissue in an animal, such as ovary and testis claimed in the instant case, remained problematic in the art, and therefore it is concluded that the unpredictability of suppressing SMCβ1 expression via antisense oligonucleotide molecules by administering the molecules to the ovary or testis was recognized in the art as of the earliest filing date sought in the instant application.

(F) The amount of direction provided by the inventor

The instant specification is silent about specific direction/guidance commensurate in scope with the claimed *in vivo* methods. That is, the specification does not provide any direction that is even remotely related to the claimed gene therapeutic invention for inducing infertility and inhibiting meiosis in a human (or animal) subject. The specification provides only generic teachings, which are entirely prophetic. Furthermore, the claimed and required method step of administering an antisense compound is not sufficiently described in the specification so as to allow one of ordinary skill in the art to practice the entire scope of the claimed invention. In fact, the word "antisense" appears only five times, on pages 2, 9, 22, 55, and 56, none of which provides a specific, useful teaching with regard to the claimed *in vivo* methods. Among those five pages, only pages 2 and 56 contain disclosure pertaining to the claimed antisense compound of 8-80 nucleotides. However, even those two occurrences in the specification are merely a general, prophetic description of antisense oligonucleotides that can be used or is contemplated to be used in the claimed methods. For example, the disclosure on page 2 states, "The compound maybe an antisense oligonucleotide" and page 56 states, "Antisense oligonucleotides which

hybridize to at least a portion of an aberrant transcript resulting from a mutation of the SMC1β gene are also contemplated by the present invention. The oligonucleotide may match the target region exactly or may contain several mismatches. Thus, molecules which bind competitively to RNA coded by, for example, SMC1β gene, for example, are envisioned for therapeutics."

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004): "Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." See also MPEP §2164.03. (emphasis added)

(G) The existence of working examples

The instant specification provides no working example commensurate in scope with the claimed methods. That is, there is no *in vivo* working example comprising the method step of administering an antisense molecule targeted to SMC1β mRNA sequence to an animal with a resultant consequence of inducing infertility in the animal. Moreover, there is not even a single *in vitro* working example demonstrating inhibitory activities of the claimed antisense SMC1β nucleic acid. Again, the relevant disclosure of the instant specification is entirely prophetic, such as "The invention also contemplate(s) the role of SMC1β *in vivo,* and its relevance for human reproductive health." See page 77" lines 22-23. In addition, there is not even a single species of antisense nucleic acids targeted to SMC1β, which has been shown to confer *in vivo* efficacy in inducing infertility. Further, given the art-recognized unpredictability of administering an antisense nucleic acid into the target cell/tissue with requisite effects as taught by Opalinska et al. and Patil et al., the absence of relevant working examples related to the claimed invention does not cure the art-recognized unpredictability of antisense gene therapy.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure

The individual assessment of the factors (A)-(G) and the combined view of the totality of the factors do suggest that one of ordinary skill in the art would not have been able to practice the entire scope of the claimed invention without undue experimentation at the time of the invention.

See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), in which it was clearly presented that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement

was appropriate, given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims.

In view of the totality of the factors listed above and the reasons stated above, the claims are rejected as failing to comply with the enablement requirement as set forth in the first paragraph, 35 U.S.C. 112.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35-39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Revenkova et al. (*Molecular and Cellular Biology,* 2001, 21:6984-6998, applicant's citation) in view of Opalinska et al. (*Nature Reviews,* 2002, 1:503-514).

The claims are drawn to an *in vitro* method of inhibiting meiosis at prophase of meiosis I in spermatocytes or oocytes by contacting the cells with a nucleic acid agent that reduces the expression or activity of SMC1β.

Revenkova et al. teach that that identified a new SMC, SMC1β, which is meiosis-specific and is found in prophase I spermatocytes. They also disclose the nucleotide and amino acid sequences of SMC1β. See the entire reference. Revenkova et al. do not teach reducing SMC1β expresion/activity, thereby inhibiting meiosis at prophase of meiosis I.

Opalinska et al. teach that nucleic acid-based agents such as target sequence-specific antisense oligonucleotides or ribozymes are used in the art to reduce target gene expression and activity in cells *in vitro*. They teach that the nucleic acid-based target gene inhibitors are useful tools for further investigating the functional roles of the target gene. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the nucleic acid-based inhibition of target gene expression/activity of Opalinska et al. to inhibit SMC1β expresion/activity, thereby inhibiting meiosis at prophase of meiosis I.

One of ordinary skill in the art would have been motivated to do so because SMC1β was newly isolated and preliminarily characterized by Revenkova et al. Since the effects of inhibiting SMC1β in germ cells have not been studied in the art, the skilled artisan knowing that SMC1β is meiosis-specific and regulates meiosis events in germ cells would have been motivated to investigate whether SMC1β is directly involved in the regulation of meiosis by inhibiting SMC1β via target gene sequence-specific nucleic acid inhibitors. Since Revenkova et al. taught that SMC1β is meiosis-specific, the skilled artisan inhibiting SMC1β expression/activity via

target gene sequence-specific nucleic acid inhibitors would have inhibited meiosis in germ cells *in vitro* at prophase of meiosis I with a reasonable expectation of success at the time of the invention. Since the knowledge and skills required to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art at the time of the invention, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
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